Translation

PATENT COOPERATION TREAT

PCT/FR2003/001851

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference BLOcp263/83P	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/FR2003/001851	International filing date (*day/month/year*) 18 juin 2003 (18.06.2003)	Priority date (*day/month/year*) 21 juin 2002 (21.06.2002)
International Patent Classification (IPC) or national classification and IPC C07K 14/36, C12P 21/04, C12N 15/68, C12Q 1/68		
Applicant COMMISSARIAT A L'ENERGIE ATOMIQUE		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
07 janvier 2004 (07.01.2004)	05 April 2004 (05.04.2004)
Name and mailing address of the IPEA/EP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/FR2003/001851

I. Basis of the report

1. With regard to the elements of the international application:*

☒ the international application as originally filed

☒ the description:

pages 1-28, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☒ the claims:

pages 1-31, as originally filed
pages _____, as amended (together with any statement under Article 19
pages _____, filed with the demand
pages _____, filed with the letter of _____

☒ the drawings:

pages 1/7-7/7, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☐ the sequence listing part of the description:

pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☒ contained in the international application in written form.

☒ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheets/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rule 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IB 03/01851

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-31	YES
	Claims		NO
Inventive step (IS)	Claims	1-31	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-31	YES
	Claims		NO

2. Citations and explanations

1. Reference is made to the following document:

D1: GONDRY MURIEL ET AL: "Cyclic dipeptide oxidase from Streptomyces noursei: isolation, purification and partial characterisation of a novel, amino acyl alpha, beta-dehydrogenase". March 2001 (2001-03), EUROPEAN JOURNAL OF BIOCHEMISTRY, VOL. 268, NR. 6, PAGES 1712-1721 XP002242439 ISSN: 0014-2956, cited in the application

2. **NOVELTY** (PCT Article 33(2))

a. D1 discloses an enzymatic activity, in *Streptomyces noursei*, which catalyses the final step in the production of albonoursin, namely the production of α,β-unsaturated residues. This enzymatic activity requires a cyclic substrate, cyclo(L-Phe-L-Leu), that does not contain a proline residue or an N-alkylated residue, and the synthesis pathway of which is unknown.

b. By studying the synthesis pathway of albonoursin, the present application has found a polynucleotide,

BamH1 (SEQ ID N° 5), including four open reading frames that each code for a polypeptide responsible for each of the steps involved in the synthesis and transport of albonoursin from L-phenylalanine and L-leucine residues in *Streptomyces noursei* and in heterologous hosts such as *Streptomyces lividans*.

c. The present application meets the requirements of PCT Article 33(2), since the subject matter of claims 1-31 is novel in view of the cited prior art.

3. **INVENTIVE STEP** (PCT Article 33(3))

a. Document D1, which is considered the closest prior art, describes an enzymatic activity that catalyses the last step in the production of albonoursin in *Streptomyces noursei*.

b. The problem that the present invention aims to solve can therefore be considered to be that of providing the synthesis pathway of albonoursin.

c. The solution to said problem would be to show that, for the synthesis of α,β-unsaturated dicetopiperazine derivatives, only the three open reading frames albA, albB and albC are absolutely essential, in particular for the synthesis of albonoursin in *Streptomyces noursei*.

d. The solution proposed in claims 1-31 of the present application is considered inventive (PCT Article 33(3)), since by studying the synthesis pathway of albonoursin, the inventors have discovered a polynucleotide, BamH1 (SEQ ID NO 5),

including four open reading frames, each coding for a polypeptide responsible for each of the steps involved in the synthesis and transport of albonoursin from L-phenylalanine and L-leucine residues in *Streptomyces noursei* and in heterologous hosts such as *Streptomyces lividans*. This solution could not be anticipated and was not obvious from the prior art documents.